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Research Article

Clinical Real-world Outcomes of Edoxaban for Venous Thromboembolism in a Single Japanese Center

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Introduction

Venous Thromboembolism (VTE), which includes Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), is a serious condition that often leads to disability and death [1]. The standard therapy for patients in Japan with acute VTE has been the administration of Unfractionated Heparin (UFH) or fondaparinux combined with a vitamin K antagonist, such as warfarin [2]. UFH is continuously given until the effect of warfarin was stabilized. Warfarin is effective but has several limitations, such as requirement of laboratory monitoring and dose adjustments, a narrow therapeutic window with an International Normalized Ratio (INR) range of 1.5-2.5, and interaction with other drugs and foods [3]. The need for frequent monitoring to assess bleeding risk and efficacy of warfarin is cumbersome for patients and physicians. Recently, the Development of New Direct Oral Anticoagulants (DOACs), which can be given in fixed doses, produce a very predictable anticoagulant response and routine coagulation monitoring is unnecessary [4]. Edoxaban has been approved in Japan as a DOAC for the treatment of VTE in 2014. Edoxaban is a once-daily, oral, direct factor Xa inhibitor. The Hokusai-VTE trial demonstrated that 60 mg of edoxaban administrated once daily after initial heparin treatment was as effective as the standard therapy in preventing the recurrence of VTE, and edoxaban administration was associated with significantly fewer bleeding events in a broad spectrum of patients with VTE [5]. Some reports described that the Asian population had higher bleeding tendencies than the Caucasian population during warfarin anticoagulation [6,7]. In addition, increases in clinically relevant bleeding with warfarin in the East Asian population may be due to differences in warfarin regulation or differences in warfarin sensitivity, as Asians tend to have higher frequencies of polymorphisms linked to the action and metabolism of warfarin. For East Asian patients with acute VTE who require anticoagulant therapy, the sub analysis of East Asian population in the Hokusai-VTE trial suggested that edoxaban is an effective and safer alternative to warfarin. These findings are consistent with the overall study results from the Hokusai-VTE trial. The number of Japanese patients who participated was 206 in a Global test, and the number of cases that took edoxaban was 106 out of 206 people [8].

Real-world data are a widely-recognized asset to provide significant additional information on drugs in clinical practice. The data obtained from the sub-analysis of Hokusai-VTE trial are from a limited group who met strict criteria for selection and exclusion. However, it is not obvious whether data from Randomized Controlled Trials (RCTs) agrees with real-world Japanese patient data because there were few real-world studies in the use of DOACs for patients with VTE in Japan. By accumulating real-world evidence, the discrepancies between the sub-analysis of Hokusai-VTE trial and real-world data are gradually reduced, and each patient enables suitable treatment. The results of RCTs may not correlate with results from real-world patients as real-world patients come from various backgrounds. In this study, we evaluated real-world patients with items similar to RCTs, and we reviewed the real-world safety and efficacy of edoxaban for patients with VTE in our institution.

Study Patients

Institutional review board approval was obtained from our hospital for this study. We retrospectively reviewed 72 patients (30 men and 42 women, mean age 64.3± 15.8 years) who were administrated edoxaban for treatment of VTE at Kurume University Hospital from January 2015 until December 2016. The standard administration of edoxaban was started after discontinuation of initial UFH, and edoxaban was administered at a dose of 60 mg orally once daily, or it was administered at a dose of 30 mg once daily in patients with a creatinine clearance of 30 to 50 ml per minute or a body weight of 60 kg or less or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors. In addition, patients who had two of the three previous conditions, or fragile or elderly patients, were administered

edoxaban at a dose of 15 mg once daily. A single drug approach, which UFH/ fondaparinux was not given as an initial treatment, was performed in the patients with calf vein thrombus or elderly patients. These are patients who can be followed up at outpatient visits. Patients were treated at the attending physician's discretion, including the use of oral antiplatelet agents or Inferior Vena Cava (IVC) filter implants.

Data Collection

We retrospectively obtained the following clinical variables from patient records: age, sex, a body weight ≤ 60 kg, Creatinine clearance (30-50 ml/min), patients with 30 mg once daily, cause of DVT, number of Japanese, details of VTE, type of DVT, medication period, and the levels of D-dimer. DVT of the calf was defined as distal DVT, and DVT of proximal side from popliteal vein was defined as proximal DVT.

Study Outcomes

The efficacy outcome was the incidence of symptomatic recurrent VTE (defined as the fatal PE, Non-fatal PE with or without DVT, or DVT alone). The primary safety outcome was the incidence of major bleeding and Clinically Relevant Non-Major (CRNM) bleeding based on ISTH criteria.

Major bleeding based on ISTH criteria was defined as the following: massive bleeding leading to fatality, symptomatic bleeding in an important organ (including intracranial, intraspinal, intraocular, retro peritoneum, the joint, pericardium, or intramuscular bleeding with compartment syndrome), intense bleeding leading to blood transfusions of more than 2 units, and reduction of more than 20 g/L of hemoglobin. CRNM bleeding was defined as a sign of bleeding not to applied to the massive bleeding of the ISTH bleeding standard, but to applied to more than one of the following items or symptoms: need for medical intervention by the clinicians, lead to hospitalization, or need for further treatment and medical examination in urgent contact with the clinicians.

Surveillance and Follow-Up

After administration of edoxaban, patients were assessed on day 7 to day 14, day 30, and day 90 by a D-dimer value. We judged the recurrence of VTE based on the measurement of D-dimer rather than a symptom. We performed imaging diagnosis using CT and US if D-dimer values were higher than the previous measurement and there was a symptom such as leg edema, dyspnea, or chest pain.

Statistical Analysis

Patient characteristics, efficacy and safety outcomes between the sub-analysis of East Asia in Hokusai-VTE trial (East Asian group) and our real-world data (Kurume group) were compared by the chi-squared test. Equivalence of two proportions/rates were examined by the TOST method [9], and 90% confidence interval on differences between two proportions/rates were reported.

Results

Baseline Characteristics

A total of 563 of 1101 patients from East Asia in the Hokusai-VTE trial were randomized and administered edoxaban. Of the East Asian patients, 209 were Japanese. 106 of 209 patients were randomized and administered edoxaban. However, the data for Japanese patients alone was not shown.

In Kurume group the number of patients who received edoxaban was 72. Patient demographic and baseline clinical characteristics were different between the Kurume group and the East Asian group. The proportion of woman (58.3% versus 51.3%), proportion of a body weight ≤60 kg (68.1% versus 33.9%), proportion of patients with 30 mg once daily (66.1% versus 41.4%) were significantly higher in the Kurume group than in the East Asian group.

The proportion of patients with temporary risk factors (63.9% versus 25.2%) and cancer (34.7% versus 9.6%) was higher in the Kurume group than in the East Asian group. The proportions of patients with unprovoked (0% versus 67.9%) and previous VTE (1.4% versus 11.2%) were lower in the Kurume group than in the East Asian group (Table 1). The proportions of patients sorted into different subsections of causes of VTE were differed greatly between the two groups.

	Kurume group (N=72)	East Asian group (N=563)	P value
Mean age (years± SD)	64.3± 15.8	61.1± 15.5	
Male n(%)	30 (41.7)	274 (48.7)	0.263
Weight< 60kg n(%)	49 (68.1)	191 (33.9)	<0.001
CrCl 30-50ml/min n(%)	11 (15.3)	81 (15.1)	0.84
Dose 30mg n(%)	44 (66.1)	233 (41.4)	0.001
Japanese n(%)	71 (98.6)	106 (18.8)	<0.001
Cause of VTE			
Unprovoked n(%)	0	382 (67.9)	<0.001
Temporary risk n(%)	46 (63.9)	142 (25.2)	
Active cancer n(%)	25 (34.7)	54 (9.6)	
Previous VTE n(%)	1 (1.4)	63 (11.2)	

Table 1: Patient Characteristics, Kurume group vs. East Asian group, VTE: Venous Thromboembolism.

The distribution of VTE before administration of edoxaban included 18 patients (25.0%) who had a PE with DVT, 4 (5.6%) who had a PE without DVT, 52 (72.2%) who had only DVT. Distal DVT and asymptomatic VTE were 38.9% and 70.8%, respectively. With regard to patient characteristics, a clear difference existed

between the Kurume group and the East Asian group since distal VTE and asymptomatic VTE were not included in the Hokusai-VTE trial (Table2).

	N=72
VTE type	
PE+DVT n (%)	18 (25.0)
PE alone n (%)	4 (5.6)
DVT alone n (%)	52 (72.2)
DVT type	
Proximal type n (%)	37 (51.4)
Distal type n (%)	28 (38.9)
Symptomatic VTE	
PE n (%)	5 (6.9)
DVT n (%)	16 (22.2)

Table 2: Details of VTE.

The median duration of administration was 165 days. No use of UFH before administration of edoxaban was only observed in 37 (51.4%) patients. The patients who received edoxaban from day 1 to day 90, from day 91 to day 180, and from day 181 to 1 year were 33 (45.8%), 7 (9.7%) and 8 (11.1%), respectively. The patients who received edoxaban longer than 1 year were 7 (9.7%). The mean D-dimer values were 10.5± 8.8 μg/ml before administration of edoxaban, but D-dimer values were gradually improved and reached 1.1± 1.0 μg/ml at 3 months. The patients who received 60 mg, 30 mg and 15 mg once daily were 15 (20.8%), 44 (66.1%) and 13 (18.1%), respectively. The patients who received edoxaban according to regular dosage and administration was 28 (38.2%) (Table 3).

	Kurume group (N=72)		East Asian group (N=563)		90% Equivalence CI on Difference
Efficacy outcome	n (%)	95%CI on %	n (%)	95%CI on %	(%)
	2 (2.8)	0.3~9.6	16 (2.8)	1.6~4.6	-5.6~5.5
Fatal PE	0		1 (0.2)		
Death with PE	0		6 (1.1)		
Non-fatal PE with or without DVT	0		5 (0.9)		
DVT alone	2 (2.8)		4 (0.7)		

Table 3: Efficacy Outcome. Fisher Exact test showed no significant difference between two proportions (p=1.0). Thus, equivalence test was carried out to examine magnitude of equivalence margin. Two efficacy outcome rates (%) were equivalent with 6% equivalence margin.

Regarding the administration of Edoxaban, the data between Kurume group and East Asian group were also different.

Recurrent VTE

Symptomatic recurrent VTE occurred in 2 of 72 (2.8%) patients in Kurume group versus 16 of 563 (2.8%) in the edoxaban treatment group from the East Asia group. Equivalent VTE recurrence rates were (2/72 and 16/563) observed between the two groups. Since 90% confidence interval on the difference rates was (-0.0561, 0.0548), the two rates were considered equivalent with margin of 6% (Table 4) and was equivalent to the standard treatment by warfarin and LWMH [8].

	N=72
Duration of drug mean days ± SD (median)	165 ±170 (90)
60mg n (%)	15 (20.8)
30mg n (%)	44 (61.1)
15mg n (%)	13 (18.1)
No pre-leading to unfractionated heparin n (%)	37 (51.4)
Discontinuation of drug within 3 months n (%)	33 (45.8)
within 6 months n (%)	7 (9.7)
within 1 year n (%)	8 (11.1)
Continuation of drug over 1 year n (%)	7 (9.7)
D-dimer pre-administration (μg/ml)	8.4
1 week after administration (μg/ml)	4.6
2 weeks after administration	3.1
1 month after administration	1.4
3 months after administration	0.8
Use of recommendation dose n (%)	28 (38.9)

Table 4: Dose, administration period and D-dimer value.

Bleeding Events

The principal safety outcome of clinically relevant bleeding (a combination of major and CRNM bleeding) occurred in 9 of 72 (12.2%) in Kurume group. 2 patients had major bleeding, including one retroperitoneal hematoma and one gastrointestinal bleeding. Both were non-fatal in a critical site. 6 patients had clinically relevant non-major bleeding. Equivalence of bleeding event rates (9/72 and 56/563) was observed between the two groups. Since a 90% confidence interval of the difference rates was (-0.0554, 0.1061), two rates were considered equivalent with margin of 11% (Table 5).

	Kurume group (N=72)		East Asian group (N=563)		90% Equivalence CI on Difference (%)
Major or non-major bleeding	n (%)	95%CI on %	n (%)	95%CI on %	
	9 (12.2)	5.9~22.4	56 (9.9)	7.6~12.7	-5.5~10.6
Major bleeding	2 (2.8)		9 (1.6)		
Fatal Non-fatal in critical sites Non-fatal in non-critical sites	0 1(1.4) 1(1.4)		0 3 (0.5) 6 (1.1)		
Clinically relevant Non-major bleeding	7 (9.7)		47 (8.3)		

Table 5: Safety Outcome. Fisher Exact test showed no significant difference between two safety proportions (p=0.53). In turn, two safety outcome rates (%) were equivalent with 11% equivalence margin.

Morbidity and Mortality

The rates of adverse events leading to permanent discontinuation of edoxaban was higher in the Kurume group than in the East Asia group {95% CI: 16.7 (8.9~27.3) vs. 2.0 (1.0~3.5), P<0.0001(2.3~ 5.4)} (Table 6). If even slight complications arose during the treatment period, we tended to go back to an administering standard therapy (warfarin overlapping UFH) because we had little treatment experience with edoxaban.

There were no deaths related to VTE during the edoxaban treatment period in the Kurume group.

	Kurume group (N=72)		East Asian group (N=563)		Difference (%) P-value * (95% CI)**
	n (%)	95%CI on %	n (%)	95%CI on %	
Any adverse event occurring during treatment period	21(29.2)	19.0~41.1	78(13.9)	11.1~17.0	0.002 (12.9~ 18.7)
Any adverse event leading to permanent discontinuation of edoxaban	9 (12.5)	5.9~22.4	17 (3.0)	1.8~ 4.8	0.0012 (2.7~ 5.9)
Any adverse event related to edoxaban Leading to permanent discontinuation of edoxaban	12 (16.7)	8.9~ 27.3	11 (2.0)	1.0~ 3.5	<0.0001 (2.3~ 5.4)

Table 6: Adverse events during the treatment period. Fisher Exact test to compare two adverse event rates. Exact p-value (*) and exact 95% confidence intervals (**) were shown in the last column.

Discussion

The efficacy of edoxaban for PE/DVT was investigated by the Hokusai-VTE examination which was an international, large-scale examination in comparing edoxaban with a standard therapy of warfarin and Low-Molecular-Weight Heparin (LMWH) [5]. A Japanese population was included in Hokusai-VTE examination, unlike global RCT of other DOACs.

In addition, a sub analysis of East Asian patients in the Hokusai-VTE trial was performed to compare differences with non-East Asian patients. There were more elderly patients in East Asian subgroup as compared with the non-East Asian subgroup, and there were more patients with a body weight <60 kg and a creatinine clearance of 30mL~50 /min in the East Asian than those in non-East Asian subgroup. East Asian patients in the Hokusai-VTE trial revealed that the recurrence rate of VTE was lower in the edoxaban group of East Asia patients than those in the edoxaban group of non-East Asian patients, and was equivalent to the standard treatment by warfarin and LWMH8. East Asian patients tended to have bleeding complications after receiving warfarin as compared with non-East Asian patients. For this reason, treatment alternatives to warfarin might be of particular relevance to this population [10]. The results of the analysis of the Hokusai-VTE trial revealed that edoxaban was associated with significantly less

clinically relevant bleeding than warfarin.

In addition, there were fewer bleeding events in the sub-analysis of East Asian patients receiving edoxaban than those receiving warfarin. The efficacy and safety of edoxaban versus warfarin were not significantly different between East Asian and non-East Asian patients.

However, RCTs are regarded the gold standard for establishing therapy effectiveness. RCTs using a standardized therapy in the chosen group of patients are typically restricted to evaluating interference of the specific respectively one by one [11].

The actual care that patients receive in clinics is recorded in real-world studies. All the patients with strict exclusion criteria in RCTs have to be treated in the real-world. Real-world data has an important role to play in the evaluation of various domains, including the clinical development of pharmaceutical products, post marketing safety, a risk benefit analysis, and medical technologies.

Japanese are at higher risk of the bleeding than Caucasians in anticoagulant therapy. Real-world data from Japanese patients are necessary safely and effectively prescribe medicines. Japanese doctors tend to prescribe anticoagulant therapies at lower dosages in the real-world because the doctors are deeply concerned about bleeding [3,12]. In our institution, prescription of 60 mg was recommended however 30 mg dosages were used 55.4% of the time, and a 15-mg dosage was used 25.7% of the time. Only 18.9% of patients received the 60-mg dose. Due to 70.3% of patients weighing less than 60 kg, there were few cases of the 60-mg dose. In addition, we reduced the dose to 15 mg from 30 mg in consideration of bleeding risk for an elderly person and feeble cases. A dose of 60 mg was used as a recommended dose in RCTs, but we often used a dose of 30 mg in the real world. It is important to choose the right dose during a suitable time period for each patient to optimize the effectiveness and safety of DOACs [13].

In RCT trials, patients with acute VTE selected for treatment with edoxaban, Subcutaneous (SC) anticoagulants (fondaparinux) or Unfractionated Heparin (UFH) are necessary for lead-in therapy. When switching from lead-in therapy, edoxaban should be initiated at the time that heparin infusions are discontinued. Other DOACs for VTE can be used in a single drug approach without a heparin lead-in. The efficacy and safety of edoxaban for the treatment of VTE in the absence of heparin treatment was not assessed in the Hokusai-VTE trial [5]. The design of the Phase Ⅲ trials with all DOACs was the treatment of symptomatic VTE [14,15]. In the real-world, patients who received edoxaban for symptomatic VTE were 23 cases (31.1%). There were a lot of non-symptomatic VTE because distal DVT was detected by examination screening.

Patients who received edoxaban without heparin for treatment of acute VTE were 48.6% in the Kurume group. Most of these cases were of distal leg DVT. Opportunities to carry out vascular ultrasounds of lower limbs increased recently because screening for VTE by the D-dimer was often performed. As a result, opportunities to detect distal DVT increased. However, the patients who had distal DVT were at high risk, including bed-ridden patients, patients with active cancer, and fragile individuals. In the guideline (2012) of the American College of Chest Physicians (ACCP) regarding anticoagulation for distal DVT, if the patients have severe symptoms they may be treated with anticoagulants. If the patients who have distal DVT with no symptoms and no risk factor for clot extension, no anticoagulants are needed. If DVT has extended, the patients are treated with anticoagulants for 3 months. If a clot extension has not occurred within the first 2 weeks, severe DVT would be unlikely to occur subsequently [16]. When the ACCP guidelines in 2012 were published, DOACs could not be used for VTE. In the guidelines on ACCP of 2016, the use of DOACs for VTE without cancer was first recommended [17]. Regarding anticoagulation therapy for distal DVT, it involves a higher risk of bleeding than effective treatment, we hesitated to administer the anticoagulant therapy in the warfarin/UFH era. For the DOACs era, because the risk of the bleeding with anticoagulant therapy decreased, we became more likely to perform anticoagulant therapy for distal DVT.

Meta-analyses of DOAC for the treatment of VTE including 3242 cancer patients described similar efficacy and safety for the DOACs compared to conventional therapy of a vitamin K antagonist in conjunction with LMWH [18, 29].

In cancer patients with DVT in the leg or PE, LMWH is suggested rather than a DOAC in the 10th ACCP guideline of 2016 [17]. However, the results of large-scale clinical trials between edoxaban and LMWH for cancer associated VTE have recently been reported, and oral edoxaban was equal to LMWH with respect to the composite outcome of recurrence VTE or major bleeding [20].

DOACs will be recommended among high-risk patients, particularly those at risk of bleeding due to an improved safety profile of DOAC in comparison with warfarin. However, it is important to emphasize the lack of experience with DOACs compared to warfarin in cancer patients who may have profound thrombocytopenia and other clinical challenges pertaining to anticoagulation. The lack of readily available measurement assays for DOACs may be particularly problematic in the setting of drug interactions, nephrotoxic chemotherapy, and potential disruption in absorption due to short bowel syndrome or malnutrition in the cancer population [21]. By our limited experience, we used DOAC for VTE due to deficiency of Protein C and HIT, but DOAC did not have efficacy and safety problems.

Regarding cancer patients, DOAC may become the first choice on ACCP for cancer-related VTE because we are unable to use LMWH for treatment of cancer-related VTE in Japan. The availability of new Direct Oral Anticoagulants (DOACs) has significantly changed the therapeutic strategies of anticoagulation, and these drugs may eventually displace standard VTE treatment with a parenteral anticoagulant overlapped with a vitamin K antagonist (e.g. warfarin) in appropriately selected patients.

Our clinical outcome showed the same efficacy and safety of initial treatment with edoxaban in patients with VTE as compared with a sub analysis of East Asian patients in the Hokusai-VTE trial. In the future, large-scale and precise investigations in the use of edoxaban in the real-world are required to validate the efficacy and safety for the treatment of VTE.

Conclusion

The safety and efficacy of DOACs were similar between our Japanese patients and East Asian population sub analyzed in the Hokusai-VTE trial, even though our Japanese patients included more women, reduced body weights, and patients were treated with lower dosages of DOAC. ACCP Guidelines in 2016 demonstrated that in patients with DVT of the leg or PE (and no cancer) suggested using a Direct Oral Anticoagulant (DOAC; apixaban, dabigatran, edoxaban, or rivaroxaban) rather than warfarin therapy. Also in Japan, DOAC was strongly recommended for VTE treatment in the new guideline of Japanese Circulation Society (JCS). There remains a need for selection of the appropriate patient, drug and dose, and careful follow up. The results of the medicine on various conditions provide guidance that may be applied to real-world practice by frontline clinicians in the future.

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